REMARKS

Claims 1-34 were pending in the present application prior to this amendment. Claims 2-16 and 20 have been withdrawn from consideration as being drawn to non-elected inventions. By virtue of this response, claims 1, 18, 21, 25, 28 and 34 have been amended, and new claims 35-95 have been added. Accordingly, claims 1, 17-19, 21-95 are currently under consideration.

Claims 18 and 34 have been amended to correct typographical errors, and to replace the term "poly(amino acid)" with an interchangeable term "polypeptide". Claims 1 and 25 have been amended to limit the high molecular weight polyethylene oxide group to having a molecular weight of at least about 18,000 Daltons, and the term "at least one" has been replaced by an interchangeable term "a". Claim 21 has been amended to recite "...wherein the biologically active molecule is a β_2GPI domain 1 polypeptide or analog thereof that specifically binds to a β_2GPI-dependent antiphospholipid antibody." Support for the claim amendments and new claims may be found at, *inter alia*, page 10 lines 16-20 (claims 1 and 25); page 37 lines 12-17 (claim 18); page 39 line 25- page 40 line 2 (claim 21); page 10 lines 16-20 and page 10 line 29 - page 11 line 3 (claim 28); page 4 lines 9-12 (claim 36); page 5 lines 5-6 (claim 37); page 5 lines 9-15 and original claims 3 and 4 (claims 38-42); page 10 lines 21-28 and original claims 5-8 (claims 43-51); page 10 lines 8-11 and original claim 2 (claim 52); original claims 9-16 and page 5 lines 26-27 (claims 53-60); page 10 lines 16-20, page 10 line 29 - page 11 line 3, page 9 lines 24-29, and page 10 lines 8-15 (claims 61-65); page 10 lines 11-13 and page 10 lines 21-28, (*i.e.* when n is 500, 520, 550, 600, 700, 800, 900, or 1000 corresponds to polyethylene oxide molecular weights of 22K, 22.9K, 24.2K, 26.4K, 30.8K, 35.2K, 39.6K, and 44.0K, respectively) (claims 66-73); page 9 lines 24-29 (claims 74-77); Figure 7, compound 203, and page 9 lines 24-29 (claim 78); page 9 lines 24-29 (claim 79); page 10 lines 11-13 and page 10 lines 21-28, *i.e.*, n

is 600 to 1000 (claim 80); page 38 lines 7-9 and page 39 line 25- page 40 line 2 (claims 81-83); Figure 7, page 10 lines 11-13, and page 10 lines 21-28, *i.e.*, n is 600 to 1000 (claim 84); page 23 line 7 – page 25 line 6 (*e.g.*, page 23 lines 9, 22-23, 26, page 23 line 29 – page 24 line 2, page 24 lines 4-8, page 25 lines 1-4 and 7-8, *i.e.*, n is 1 to 500), page 9 lines 24-29 and page 10 lines 8-15 (claim 85); page 23 line 7 – page 24 line 2, page 24 lines 19-23, and page 25 lines 1-6 (claims 86-87); page 26 line 1 – page 28 line 11, and page 34 lines 7-10 (claims 88-89); page 30 line 4 – page 32 line 15, and page 34 lines 7-10 (claims 90-91); page 14 line 12 – page 16 line 19, page 21 lines 16-18, page 21 line 21 – page 22 line 15, page 11 lines 11-19, and page 43 lines 15-22 (claims 92-93); and page 18 line 29 – page 21 line 3, page 21 lines 16-18, page 21 line 21 – page 22 line 15, page 11 lines 11-19, and page 43 lines 15-22 (claims 94-95).

No new matter is believed to have been introduced by the amendments.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiment in future continuation and/or divisional applications.

Claim 1 is drawn to chemically defined valency platform molecules which comprise a (*i.e.*, at least one) high molecular weight polyethylene oxide group. Claims 17-19, 21-95 are drawn to conjugates of valency platform molecules and biologically active molecules. Applicant appreciates the examination of the claims currently under consideration as an administrative convenience in expediting prosecution and understands that no conclusions are drawn as to the presently considered claims defining more than one invention.

Rejections under 35 U.S.C. § 112, 2nd paragraph

The Office has rejected claims 1 and 21 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully traverses these rejections.

In order to promote prosecution, claim 1 has been amended to include the limitation "comprising a high molecular weight polyethylene oxide group having a molecular weight of at least about 18,000 Daltons".

Applicant submits that the term "analog" as used in claims 21 and 23 is a definite term well known to those of skill in the art, used to describe a compound or molecule which performs a similar function. For example, claim 23 describes an "analog" of an αGal epitope functionally: "...wherein the biologically active molecule is an αGal epitope or analog thereof *that specifically binds to an anti-αGal antibody* [emphasis added]." In order to promote prosecution of the application, Applicant has amended claim 21 to recite "...wherein the biologically active molecule is a β_2GPI domain 1 polypeptide or analog thereof that specifically binds to a β_2GPI-dependent antiphospholipid antibody." This amendment does not narrow the scope of the originally claimed subject matter.

Accordingly, Applicant respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 112, 1st paragraph

The Office has rejected claims 21 and 23 as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses this rejection.

As stated above, one of ordinary skill in the art would understand what the term "analog" comprises. Further, the claims as amended recite that the analogs of domain 1 β_2GPI polypeptides and αGal epitopes have antibody binding properties of domain 1 β_2GPI polypeptides and αGal epitopes, in that they specifically bind to β_2GPI-dependent antiphospholipid antibodies or anti-αGal antibodies, respectively. One of ordinary skill in the art would understand that there may be a variety of permutations encompassed by the term "analog," including, for example, peptides, saccharides, nucleic acids, and lipids. Page 39 line 25-page 40 line 2 of the specification describe one possible permutation of analogs of domain 1 β_2GPI polypeptides: "It is also understood that certain sequence variations may be introduced into a domain 1 β_2GPI polypeptide which may preserve or enhance its reactivity. These variant and modified sequences are collectively denoted as "functionally equivalent variants", which may have the same, enhanced, or diminished binding when compared to another domain 1 β_2GPI polypeptide, and are denoted "equivalent" because they maintain the ability to specifically bind to a β_2GPI-dependent antiphospholipid antibody."

Accordingly, Applicant respectfully requests that the rejections under 35 U.S.C. § 112, 1st paragraph be withdrawn.

Rejections under 35 U.S.C. § 103(a)

The Office has rejected claims 1, 17-19 and 21-31 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Iverson *et al.* (hereafter Iverson) in view of Lanza *et al.* (Patent No.

6,368,612 B, issued April 9, 2002, hereafter Lanza). Applicant respectfully traverses the rejection.

Iverson relates to a tetrameric organic platform conjugate for multivalent presentation of a peptide epitope for human anti-β_2GPI antibodies. Iverson teaches that this conjugate may be useful as a toleragen in patients with antiphospholipid syndrome. As noted by the Examiner, Iverson does not specifically teach polyethylene oxide, αGal epitope, β_2GPI domain 1 polypeptide, at least 3 carbamate groups, at least five contiguous amino acids or amino acids 2-63 of SEQ ID NO. 2, or compounds 200, 202, 203, 205, and 300. Applicant notes that Iverson does not refer to the peptides disclosed in the reference as β2GPI domain 1 polypeptide analogs. Iverson does not teach a chemically defined valency platform molecule comprising a (*i.e.*, at least one) high molecular weight polyethylene oxide group having a molecular weight of at least about 18 kDa.

Lanza does not teach a chemically defined valency platform molecule comprising a (*i.e.*, at least one) high molecular weight polyethylene oxide group having a molecular weight of at least about 18 kDa. Instead, Lanza relates to implantable and extracorporeal devices for cloaking a source of a therapeutic substance, such as living cells, which source provides the substance to a host. Lanza teaches that in such devices, host molecules can attack the source of the therapeutic substance and impair the function of the device; semipermeable components may be used to inhibit the ability of host molecules to enter the device and attack the source of the therapeutic substance (col. 1 line 54-64). Lanza teaches the use of high molecular weight polyethylene oxide (PEO) to control porosity of the microparticles containing the living cells of the device, in order to prevent entry of substances such as antibodies from the host into the microparticles (col. 13, lines 50-66). Lanza also teaches that PEO or polyethylene glycol (PEG) may be used in other

compartments of the device, such as the super matrix, in order to impede the passage of host-derived molecules or cells (col. 25 lines 46-54). Lanza teaches that the PEO groups may be of molecular weight 1-8 million Da (1,000 – 8,000 kDa) (col. 13 lines 63-66), or greater than 8,000 kDa (col. 15 lines 48). Lanza also teaches the inclusion of a rescue agent in the device, such as αGal epitopes, in order to inhibit the ability of a host molecule to damage donor, *e.g.*, implanted tissue (col. 44 lines 10-12, col. 45 lines 25-26).

Applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the reference (or references when combined) must teach or suggest all the claim limitations. These requirements are summarized in the MPEP (MPEP §2143, and §2143.01 to §2143.03), and are based on well-settled case law: *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Applicant respectfully submits that there is no motivation to combine these references. There is no suggestion in Iverson or Lanza to combine high molecular weight PEO or PEG groups with chemically defined valency platform molecules, which may be used to form conjugates useful for treating, *e.g.*, antiphospholipid syndrome. Further, one of skill in the art would not be motivated to combine the PEO groups of 1,000 kDa or more of Lanza, used in Lanza for controlling the porosity of a device which releases a therapeutic substance, with the platform molecules of Iverson, which Iverson teaches may be used to make conjugates for use as

B cell toleragens in treating antiphospholipid syndrome, in order to create a chemically defined valency platform molecule comprising a high molecular weight polyethylene oxide group of at least about 18 kDa, as claimed in independent claims 1 and 25 and dependent claims 17-19, 21-24 and 26-31. As the filtering function of the PEO and PEG groups disclosed in Lanza is not analogous to the function that PEO or PEG groups would have in a platform molecule for treating antiphospholipid syndrome, one of skill in the art would therefore not be motivated to combine the teachings of Lanza and Iverson. As such, the obviousness rejection may be properly withdrawn on this ground.

Further, even if combined, Lanza and Iverson do not teach or suggest all of the claim limitations. The combination of Iverson and Lanza merely provides a device containing high molecular weight PEO or PEG groups which are used to control porosity and a conjugate that does not contain high molecular weight PEG (with no disclosure or suggestion to use high molecular weight PEG), not a conjugate containing high molecular weight PEG. This combination is not the invention. As such, the obviousness rejection may be properly withdrawn on this ground.

Applicant submits that the claims are not obvious for the reasons given above. Additionally, there is no suggestion in Lanza or Iverson to combine αGal epitopes or analogs thereof with chemically-defined valency platform molecules, or chemically-defined valency platform molecules comprising a high molecular weight PEO group, as in claim 23.

Even if combined, Lanza and Iverson do not teach all of the claim limitations. As noted above, both Lanza and Iverson are silent with respect to connecting a high molecular weight PEG to a valency platform molecule. Further, both Lanza and Iverson are silent with respect to connecting an αGal epitope with a platform molecule.

There is further no suggestion in Iverson, in combination with Lanza, of conjugates comprising a chemically defined valency platform molecule and a polypeptide comprising a β_2GPI domain 1 polypeptide, wherein the valency platform molecule comprises a high molecular weight polyethylene oxide group, wherein the high molecular weight polyethylene oxide group has a molecular weight of at least about 18 kDa, as claimed in independent claim 25 and dependent claims 26-31. There is also no suggestion in Iverson, in combination with Lanza, of conjugates comprising a chemically defined valency platform molecule and a polypeptide comprising a β_2GPI domain 1 polypeptide or analog thereof, wherein the valency platform molecule comprises a high molecular weight polyethylene oxide group, wherein the high molecular weight polyethylene oxide group has a molecular weight of at least about 18 kDa, as claimed in claims 21 and 22.

Thus, Applicant submits that the claims are not obvious in view of Iverson in combination with Lanza.

The Office has rejected claims 32-34 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Iverson in view of Lanza, further in view of Matsuura *et al.* (Patent No. 5,998,223, issued December 7, 1999, hereafter Matsuura). Applicant respectfully traverses the rejection. Applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness.

As noted by the Examiner, Iverson does not specifically teach a β_2GPI domain 1 polypeptide, or at least five contiguous amino acids or amino acids 2-63 of SEQ ID NO. 2.

Claims 32-34 depend from claim 25, which claims conjugates comprising a chemically defined valency platform molecule, wherein the valency platform molecule comprises a high molecular weight polyethylene oxide group having a molecular weight of at least about 18 kDa.

As noted above, Iverson and Lanza provide no motivation to combine platform molecules with high molecular weight polyethylene oxide groups, and further, that even in combination Iverson and Lanza do not teach the claimed invention.

Matsuura does not cure the deficiencies of Iverson and Lanza. Matsuura relates to methods for assaying an anticardiolipin antibody from patients with antiphospholipid syndrome. Using deletion mutants of the β_2GPI protein to determine to functionality of domains I-V of β_2GPI, Matsuura concluded that (1) the phospholipid binding site is present in domain V; (2) the epitope which is recognized by the autoantibody from patients with antiphospholipid syndrome is present in a region centering around domain IV; and (3) this epitope is usually cryptic, but domain V binds to phospholipid or the like, resulting in that the mutant protein undergoes a conformational change, whereby the epitope is exposed to be recognized by the autoantibody (col. 20 lines 48-61). Matsuura teaches three methods for assaying antiphospholipid antibodies; Methods 1 and 3 use, in place of β_2GPI itself, a polypeptide containing the same amino acid sequence as domain IV and V of β_2GPI or a polypeptide partially different therefrom but functionally equivalent thereto; and Method 2 uses, in place of β_2GPI itself, a polypeptide containing the same amino acid sequence as domain IV of β_2GPI and not containing the same amino acid sequence as domain V of β_2GPI or a polypeptide partially different from but functionally equivalent thereto (col. 5 lines 25-50).

Matsuura does not teach or suggest that domain 1 of β_2GPI may bind to antiphospholipid antibodies, as in the instant invention; if anything, Matsuura teaches away from using domain 1 of β_2GPI to bind antiphospholipid antibodies by teaching that domain IV is the active part of the molecule.

From the teachings of Iverson, Lanza, and Matsuura, there would be no motivation to combine a polypeptide of domain 1 of β_2GPI or analogs thereof with a chemically defined valency platform molecule comprising a high molecular weight polyethylene oxide group having a molecular weight of at least about 18,000 Da. In particular, there would be no motivation for one of skill in the art to combine a polypeptide comprising at least five contiguous amino acids of SEQ ID NO:2 or a polypeptide comprising amino acids Nos. 2-63 of SEQ ID NO:2 with chemically defined valency molecules comprising at least one high molecular weight polyethylene oxide group having a molecular weight of at least about 18,000 Da, as claimed in claims 32-34. Even in combination, Iverson, Lanza and Matsuura do not teach or suggest all of the claimed limitations.

Thus, Applicant submits that the claims are not obvious in view of Iverson, in view of Lanza and further in view of Matsuura. Accordingly, Applicant respectfully requests that the rejections under 35 U.S.C. § 103(a) be withdrawn.

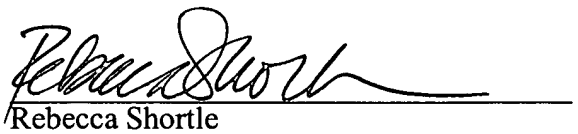
CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, addressed all issues that were raised in the outstanding Office Action. Applicant respectfully contends that this Amendment has overcome the rejections and that the pending claims are in condition for allowance. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 252312007500.

Respectfully submitted,

Dated: July 10, 2003

By: 

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